Emerging Biotechnologies: Challenges Raised for Our Current System of Biosafety Oversight by Gene Drive

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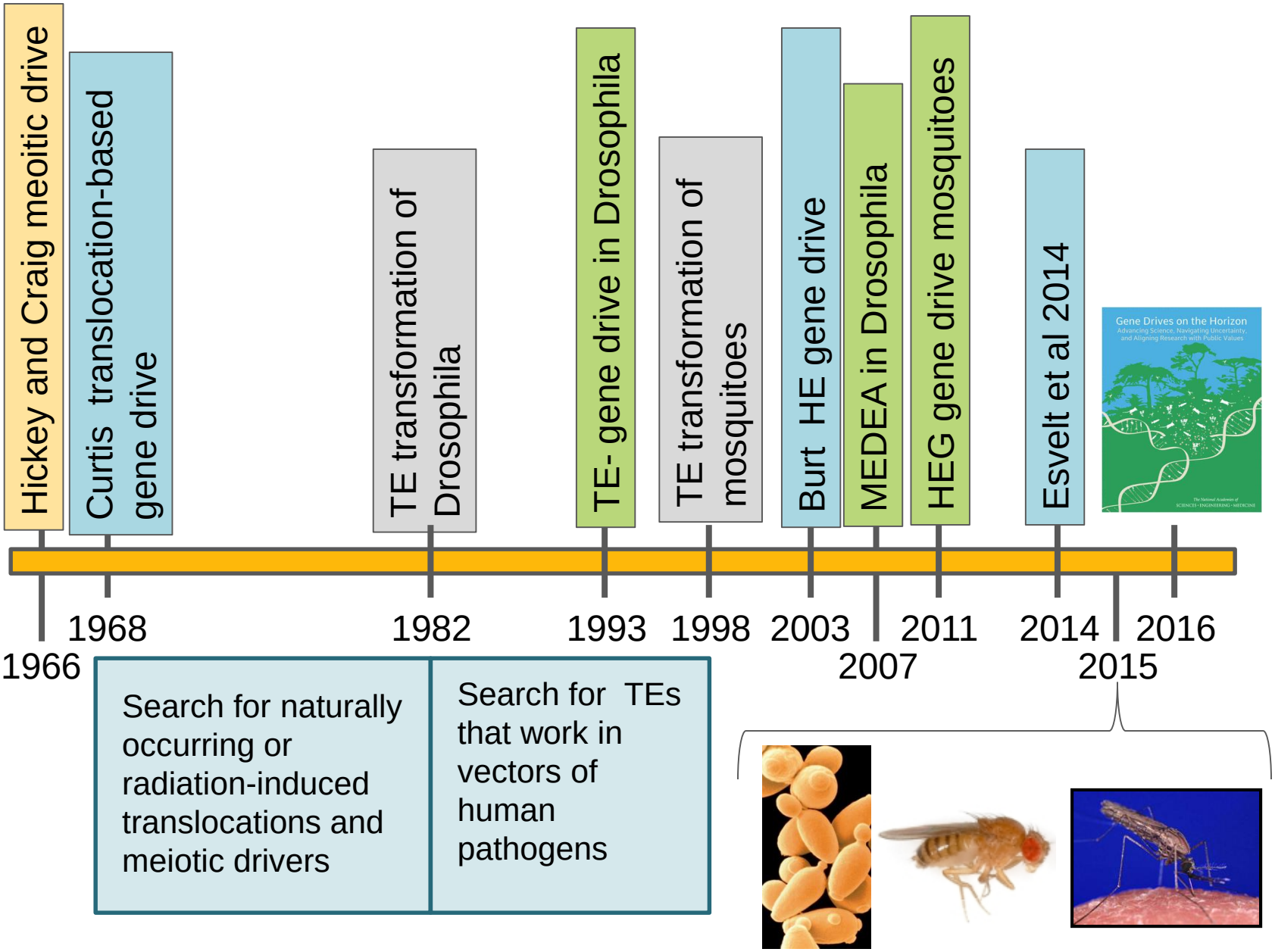
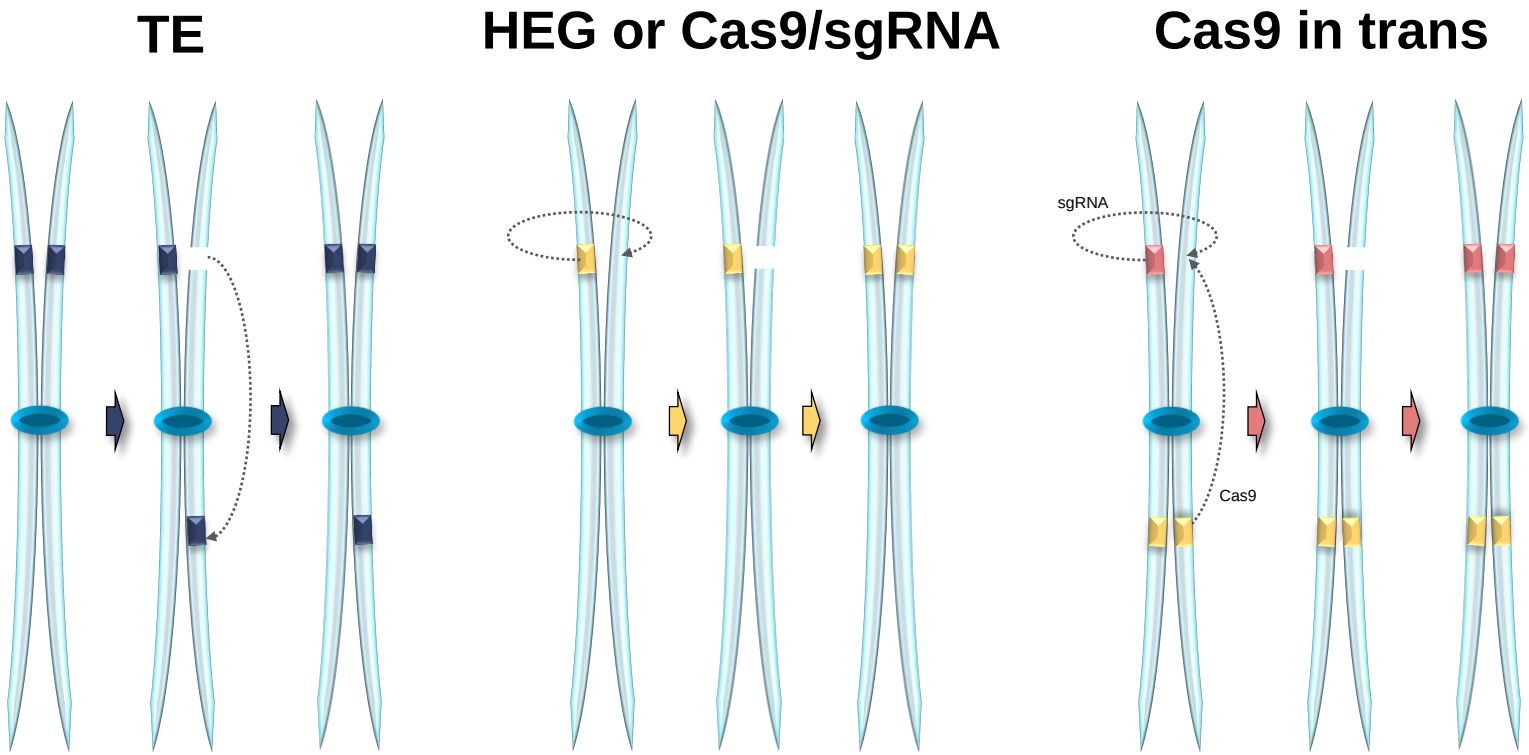
Timeline of laboratory research of gene drive



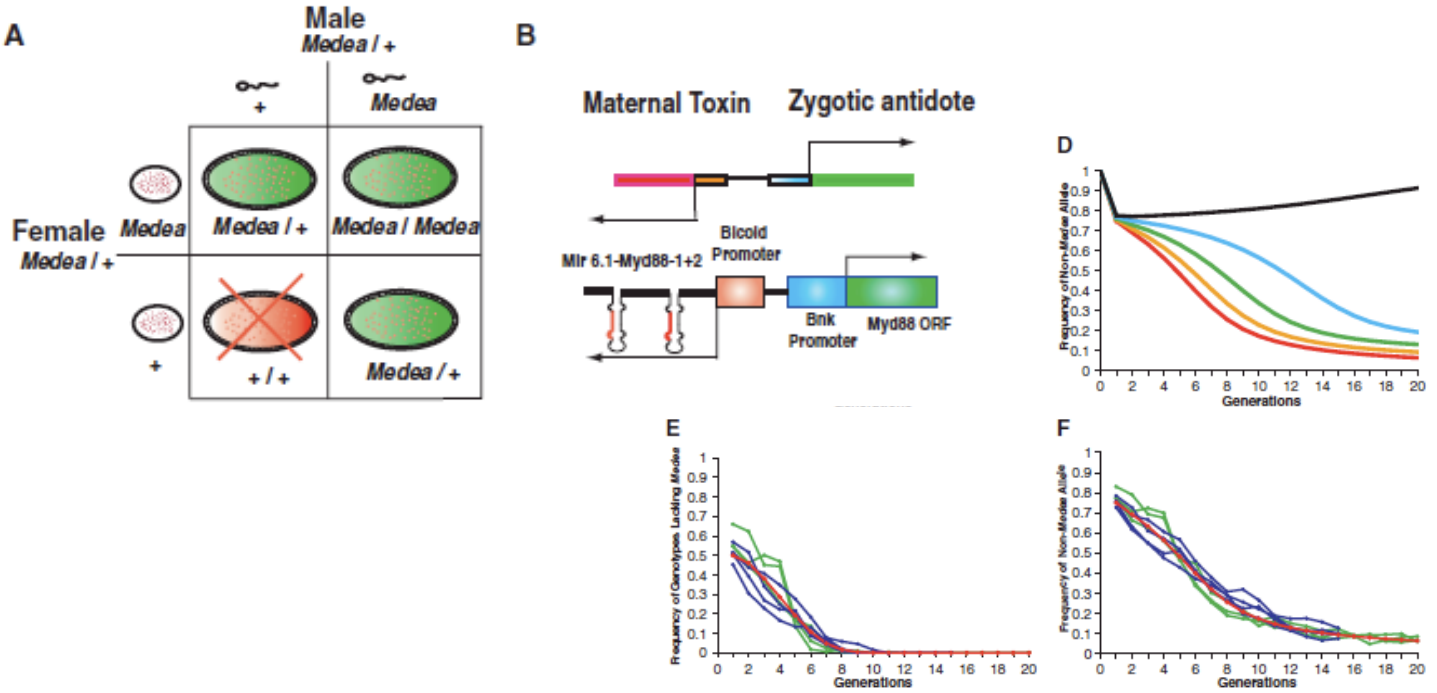
Cut/Repair gene drives



Adelman and Tu. Control of Mosquito-Borne Infectious Diseases: Sex and Gene Drive. Trends in Parasitology, March 2016, Vol. 32, No. 3

A Synthetic Maternal-Effect Selfish Genetic Element Drives Population Replacement in *Drosophila*

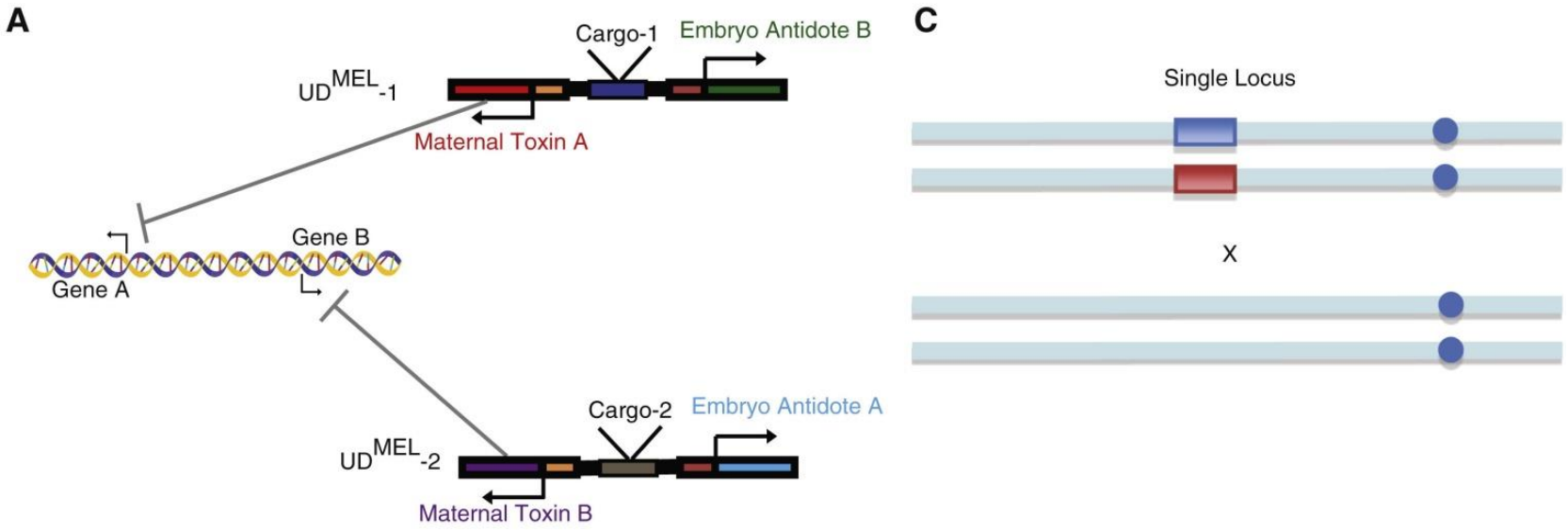
Chun-Hong Chen,[1] Haixia Huang,[1] Catherine M. Ward,[1] Jessica T. Su,[1]
Lorian V. Schaeffer,[1] Ming Guo,[2] Bruce A. Hay[1]*



Concept can be adapted for targeting any maternally deposited transcript vital for embryo survival; Very stable, highly invasive.

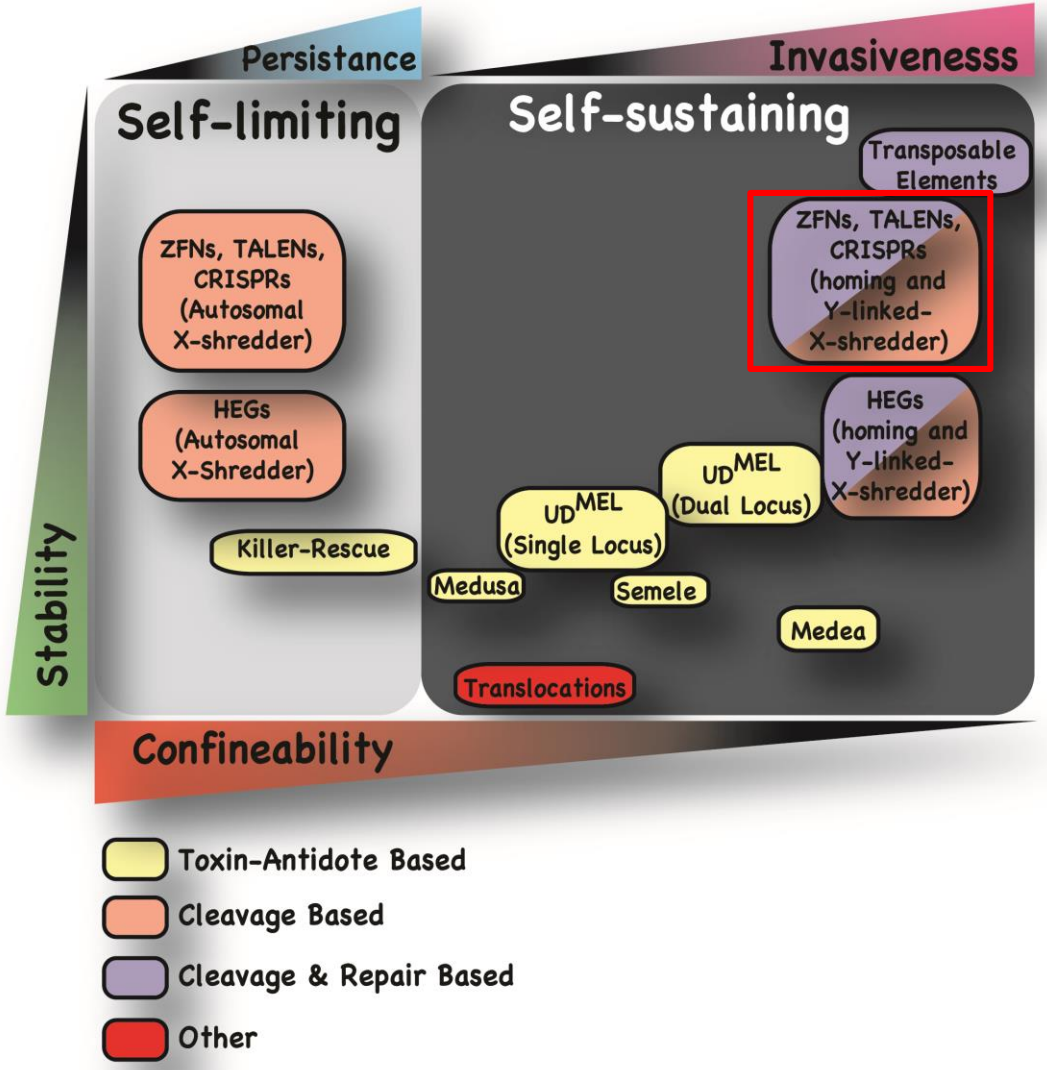
Engineered underdominance (UD^{MEL})

Akbari et al Current Biology 23, 671–677, April 22, 2013



More stable than cut/repair strategies, high threshold simplifies containment.

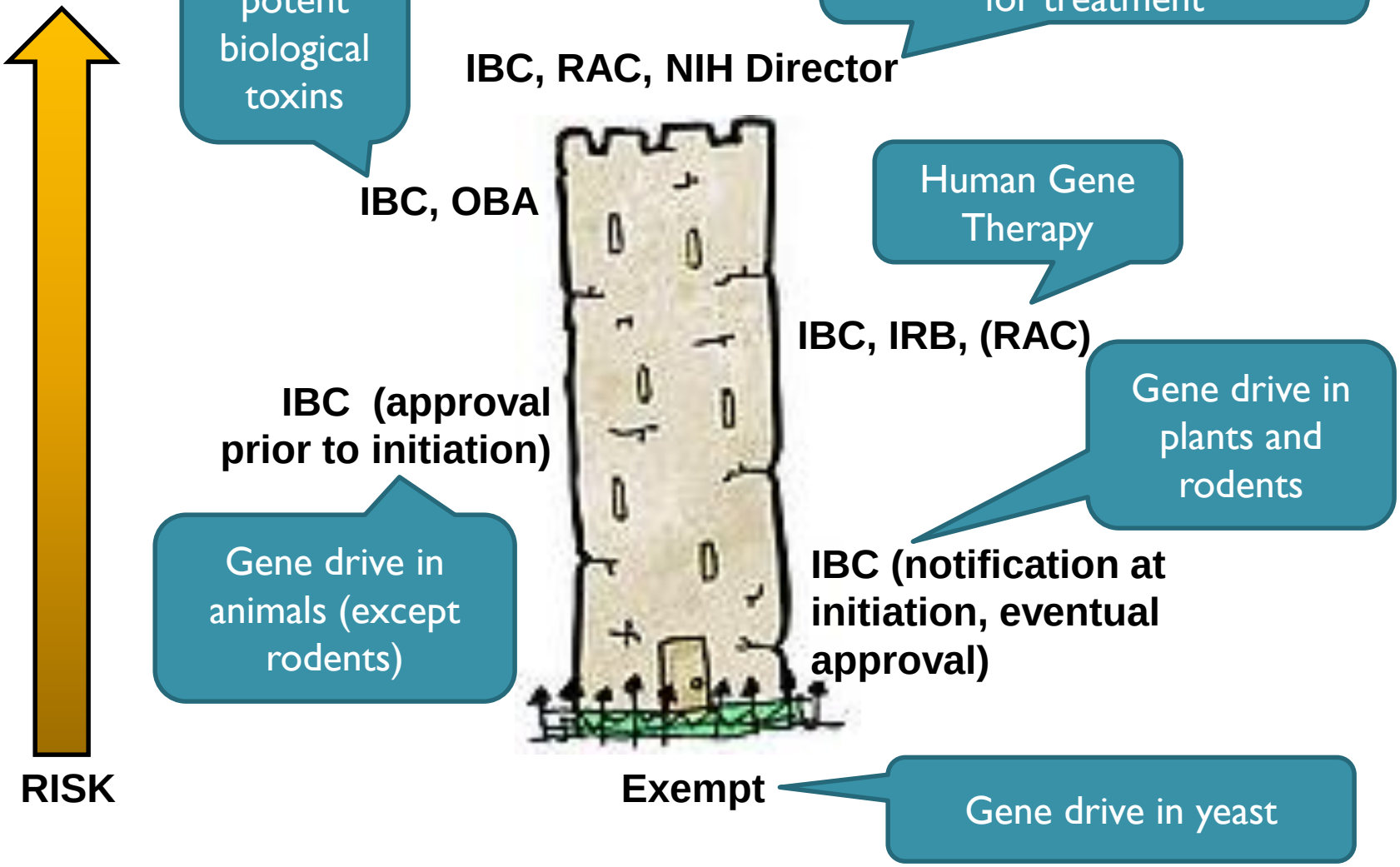
Many diverse molecular genetic strategies to achieve gene drive



Gene drive is not just CRISPR!!!

From: Marshall and Akbari (2015) Gene Drive Strategies for Population Replacement; Genetic Control of Malaria and Dengue, Elsevier.

The (current) tower of risk



Section III-D-4: Experiments involving whole animals

Gene drives in animals (except rodents) fall into this category and <u>REQUIRE</u> IBC approval before beginning any work

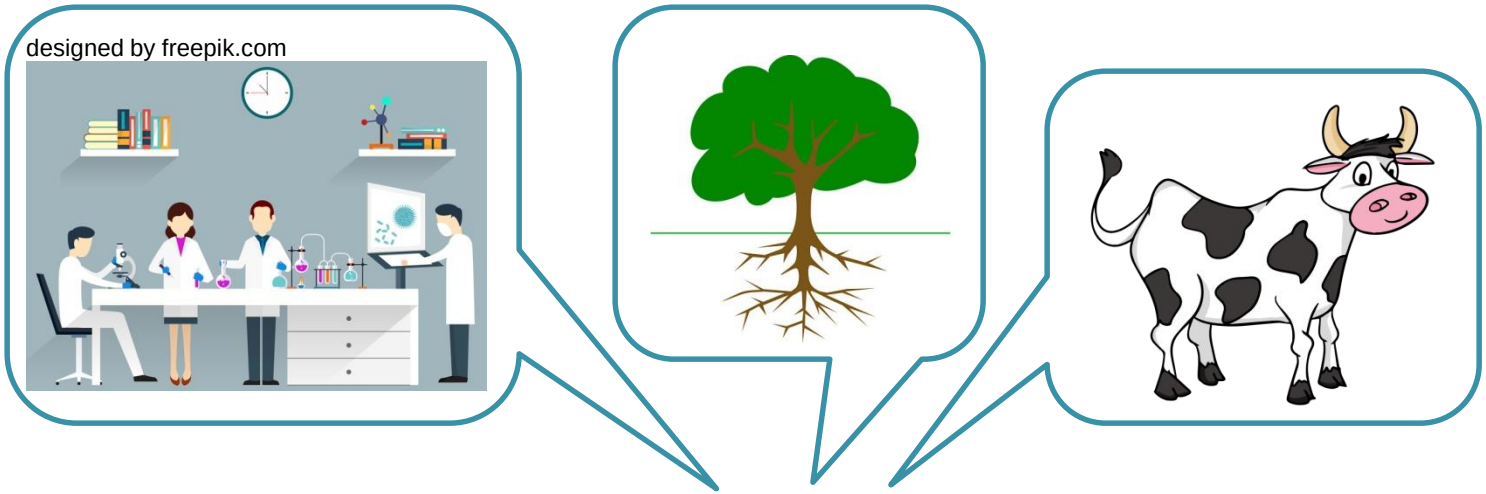
Most will fall under BL1 containment: not sufficient for many gene drive types!!!

Risk assessment for laboratory gene drive research

Gene drive

Section V-M. Determination of whether a ~~pathogen~~ has a potential for serious detrimental impact on managed (agricultural, forest, grassland) or natural ecosystems should be made by the Principal Investigator and the Institutional Biosafety Committee, in consultation with scientists knowledgeable of ~~plant diseases, crops~~, and ecosystems in the geographic area of the research. ???

Containment practices



- **Physical (Appendix G, P, Q)**
  - **Practices**
  - **Equipment**
  - **Facilities**
- **Biological (Appendix I)**
  - **Survival**
  - **Transmission**

No specific guidance for arthropod containment

Modified from: NIH/OBA

Arthropod Containment Guidelines

- Developed by a subcommittee of the American Society of Tropical Medicine and Hygiene in 2003.
- Containment levels 1-4 to mirror handling pathogen-infected arthropods (based on agent BSL)
- Containment ACL-2 designated for genetically-modified arthropods.
- ACG do not mention gene drive, but current interpretations utilize ACL-2 as well.

ACG are not binding and may or may not be utilized by PIs/IBCs

Drosophila, are in fact, arthropods

"Akbari et al. call for stringent regulation of research using *Drosophila melanogaster* on "gene drives," genetic constructs that at least in a laboratory setting can increase their inheritance above simple Mendelian expectation. The new proposed regulations would include prior committee approval, restrictive laboratory design not readily available in most institutions, and time-consuming biological containment."

GSA Public Policy Chair Allan Spradling

http://genestogenomes.org/gene-drive-more-research-not-more-regulations/

Containment for gene drive research

The PI *suggests* containment conditions and SOPs to the IBC.

The IBC *sets* containment and vets SOPs as part of the approval process.

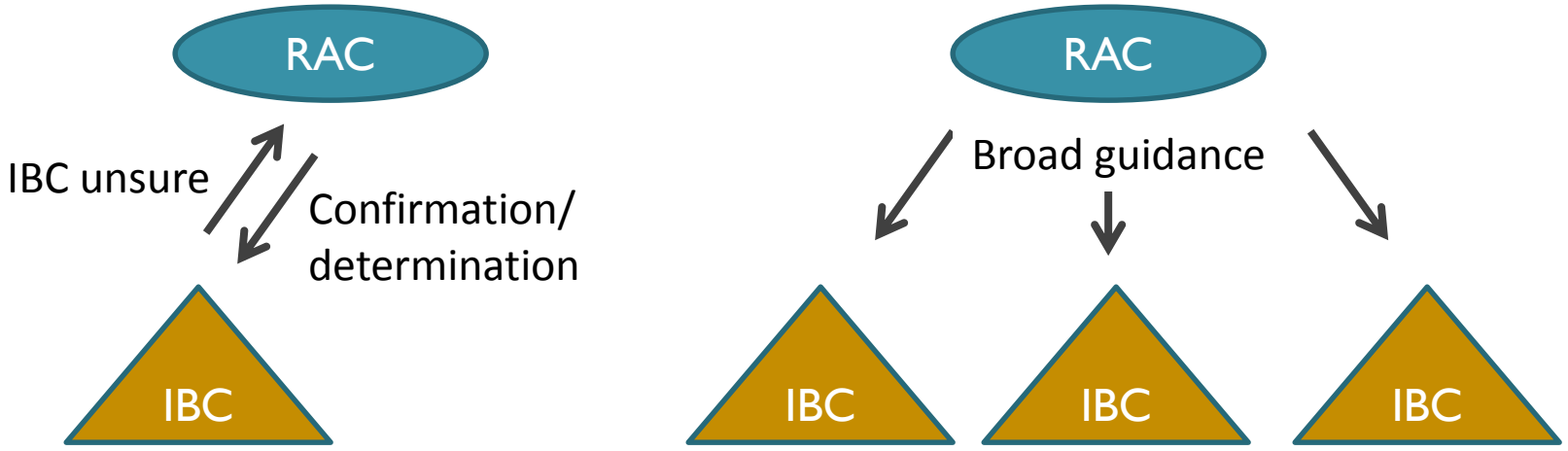
Containment conditions/work practices are verified by inspections (EHS/BSO) and cannot be changed by the PI without IBC approval (amendment)

Is there a biosafety officer?

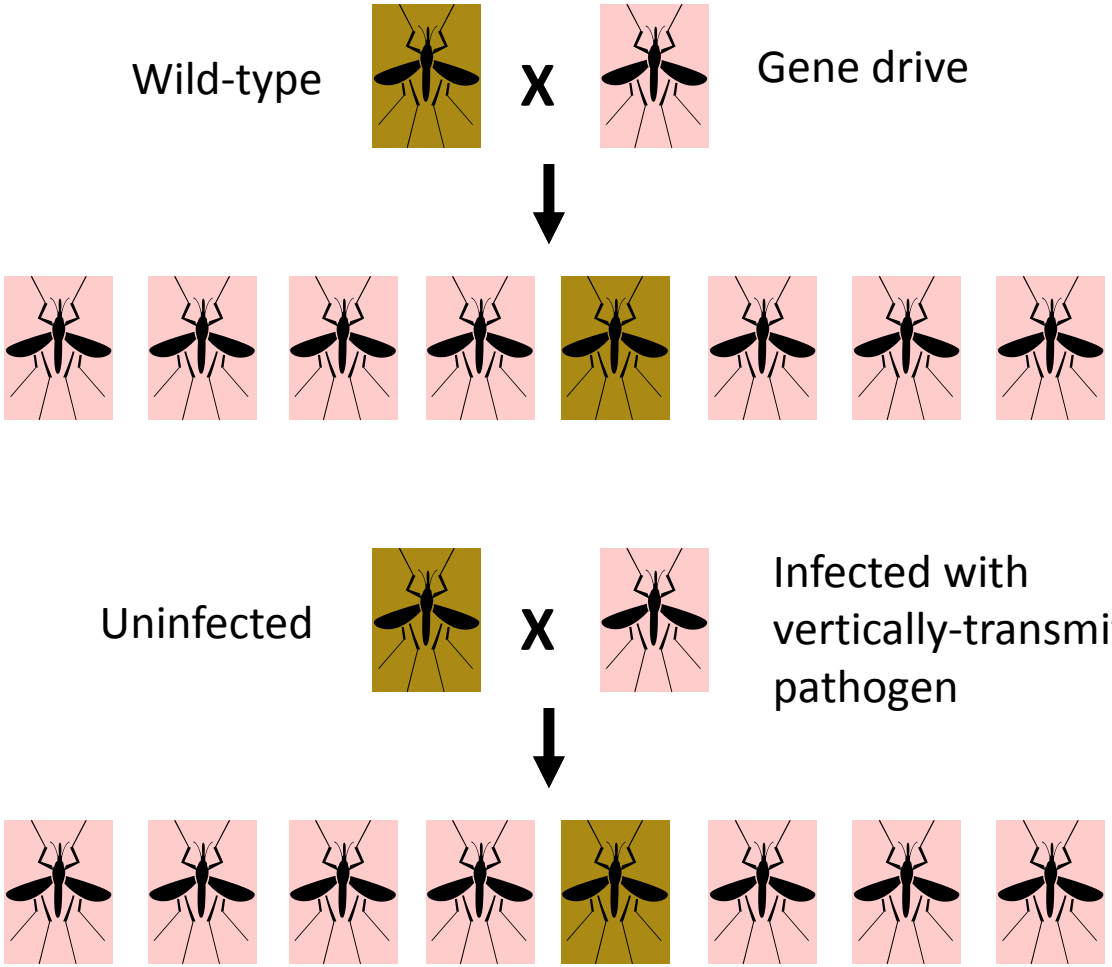
NIH guidelines require institutions to have a BSO if they perform any work at BSL3/ABSL3 or above or large scale activities (>10L).

BSO is a permanent member of the IBC and serves as valuable resource in the establishment and review of research protocols including laboratory inspections.

Should RAC have a role in setting containment of gene drive research?



Is there a precedent for gene drive in the world of biocontainment?



Summary

Gene drive refers to introduced genetic material capable of increasing its frequency in a given population in spite of providing no benefit or even a fitness detriment

NIH Guidelines currently regulate most, but not all laboratory gene drive experiments, but treat them no differently than other recombinant DNA (BL1).

While IBCs may not have experience with self-propagating gene drives, thinking of these as infectious agents (transmitted vertically) reveals some parallels in lab construction and containment.

In contrast, PIs proposing such experiments may have no experience working under higher containment levels.

Challenges for IBC review of gene drive research

Gene drives present no risk to the health and safety of laboratory workers and thus may not be given as thorough a review as pathogen-based work or human gene therapy.

Some types of gene drive research are currently exempt from the NIH guidelines and thus are not reviewed by the IBC.

No specific guidance on containment for arthropods, biosafety officer may not be present.

NIH guidelines apply NIH-funded entities only.

A updated starting point for risk assessment of laboratory-based transgenic organisms

- Is the introduced trait (or combination of traits) likely to persist or spread through a natural population if introduced?
  - Yes: includes some gene drives but also Mendelian traits that provide a net benefit
  - No: includes some gene drives but also traits that are neutral or confer a disadvantage

IBCs should review all work prior to initiation involving recombinant DNA capable of spreading into a population

Move these experiments to a new "Section III-D-?".

Section III-E-1. Experiments Involving the Formation of Recombinant or Synthetic Nucleic Acid Molecules Containing No More than Two-Thirds of the Genome of any Eukaryotic Virus

Section III-D-3. Experiments Involving the Use of Infectious DNA or RNA Viruses or Defective DNA or RNA Viruses in the Presence of Helper Virus in Tissue Culture Systems

Section III-E-2. Experiments Involving Whole Plants (BL1-P)

Section III-D-5. Experiments Involving Whole Plants (BL2-4P)